Remarks

Upon entry of the foregoing amendment, claims 136-149 are pending in the application, with claim 136 being the independent claim. Claim 136 is sought to be amended. Claims 148 and 149 are sought to be added. Support for the amendments to claim 136, and new claims 148 and 149 may be found, *inter alia*, at p. 45 of the specification, and therefore does not introduce new matter.

The specification has been amended to indicate that a benefit application has issued as a U.S. patent.

Based on the above amendments and the following remarks, Applicant respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Sequence Compliance

The Examiner indicated that the application contains several figures that recite nucleotide sequences that must comply with rules set forth in 37 C.F.R. 1.821 through 1.825. Applicant has amended the specification to insert the sequence identifiers and note that the sequences identified by the Examiner and the Applicant are present in the sequence listing as filed. Accordingly, Applicant requests reconsideration and withdrawal of the requirement to submit a computer readable form containing the SEQ ID numbers and paper copy of the sequence listing.

Rejections under 35 U.S.C. § 112

The Examiner rejected claims 136, 137, 145 and 146 as allegedly indefinite for reciting the phrase "abortive reiterative synthesis," stating that the specification does not explicitly define what constitutes an abortive reiterative synthesis, so as to properly determine the metes and bounds embraced by this limitation. Applicant respectfully traverses this rejection.

Applicant respectfully disagrees with the Examiner that "abortive reiterative synthesis" is indefinite. The specification describes "abortive transcription," which is an embodiment encompassed by the claims, as follows:

> "[a]bortive transcription" is an enzyme-mediated process that reiteratively initiates and terminates the synthesis of oligonucleotides that correspond to at least one portion, or target site, of a complementary nucleic acid template sequence. The abortive oligonucleotides synthesized vary in length of nucleotides, and may contain from about 2 to about 26 nucleotides, about 26 to about 50 nucleotides and about 50 nucleotides to about 100 nucleotides, and greater than 100 nucleotides.
>
> "Abortive transcription" also includes three phases, namely, initiation, elongation, and termination. During the initiation phase, a polymerase forms a phosphodiester bond between an initiator and a second NTP, and then adds subsequent NTPs, *et cetera.*, transcribing the template sequence to synthesize an oligonucleotide transcript of from about 2 to about 50 nucleotides in length and then terminating the transcription event by releasing the nascent oligonucleotide transcript, without the polymerase substantially translocating from the polymerase binding site or dissociating from the template. In other words, the RNA polymerase substantially remains at the initial binding site on the template, releases a first nascent oligonucleotide transcript, and then is capable of engaging in another transcription initiation event to produce a second oligonucleotide transcript, which is substantially complementary to substantially the same target site that was transcribed to produce the first oligonucleotide transcript. In this manner, the polymerase reiteratively transcribes a single portion of the template (*i.e.*, a target

> region) and releases multiple copies of substantially identical nascent oligonucleotide transcripts.

Specification at p. 31-32. The specification describes "reiterative" as referring to "multiple identical or highly similar copies of a sequence of interest." *Id.* at p. 31.

The specification describes that the abortive reaction can be controlled such that the polymerase aborts synthesis after extension of even just one nucleotide. *Id.* at p. 72-79. For example, if the genetic sequence of the target site is known, a chain terminating nucleotide analog corresponding to a nucleotide that is complementary to a nucleotide at a specific position on the target site can be added to the reaction mixture. In this manner, synthesis is aborted after extending by a predetermined number of nucleotides, yielding products of the same, predetermined size. Therefore, Applicant respectfully submits that the specification describes what is encompassed by an abortive reiterative synthesis so as to properly set forth the metes and bounds embraced by this limitation. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

The Examiner further rejected claim 146 as allegedly indefinite stating that the claim recites that the target molecule being detected is a protein, while the detection method is achieved by detecting multiple copies of detectable oligonucleotides (*i.e.* nucleic acid). Applicant respectfully traverses this rejection.

Applicant respectfully submits that the claim is not indefinite. The specification describes an embodiment in which the target molecule being detected is a protein. The target protein can be labeled by covalent or noncovalent attachment of a defined nucleic acid sequence which can be used for reiterative oligonucleotide synthesis. See p. 48-49 of the specification. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Rejection under 35 U.S.C. § 102

The Examiner has rejected claims 136-138, 140, and 145-147 under 35 U.S.C. § 102(b) as allegedly anticipated by Sasaki *et al.* (*Proceed Nat Acad Sci USA*, 95:3455-3460 (1998)). The Examiner also rejected claims 136-139, 141-145 and 147 under 35 U.S.C. § 102(b) as allegedly anticipated by Daube *et al.* (*Science*, 258:1320-1324 (1992). Applicant respectfully traverses these rejections.

Under 35 U.S.C. § 102, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

1. Rejection over Sasaki et al.

The Examiner contends that Sasaki *et al.*, as demonstrated by Figure 4 on p. 3457, teaches an abortive reiterative synthesis reaction wherein the abortive reaction is achieved by incorporation of four kinds of dye-3' dNTPs. See Office Action, p. 3.

The Applicant respectfully disagrees with the Examiner's characterization of Sasaki *et al.* Applicant respectfully submits that Sasaki *et al.* does not disclose an "abortive reiterative synthesis" reaction.

As noted above, according to the Applicant's specification, "reiterative" refers to "multiple identical or highly similar copies of a sequence of interest." Sasaki *et al.* report a sequencing method using RNA polymerase, referred to as "transcriptional sequencing." See p. 3455. Sasaki *et al.* use four color dye-3'-dNTPs as dye terminators in the reaction. *Id.* Use of four dye-dNTP terminators allows the reaction to be run in a single tube and generates sequencing products that are heterogeneous in size. The dye terminators are present in low amounts in the reaction relative to unlabelled dNTPs and therefore

incorporate at a specified position in only a small percentage of transcripts. This generates transcripts that are heterogeneous in size and allows for individual fragments to be separated by electrophoresis. In this manner, the nucleotide at each base position can be determined. The fragments range in size from about the size of the primer (usually about 20 nucleotides) to greater than several hundred bases in length. Sasaki *et al.* report a transcriptional sequencing reaction which generate fragments that range up to at least 600 nucleotides in length. See Fig. 5A. Clearly, such heterogeneous fragments are not the products of a reiterative process because they are not "identical or highly similar copies." Therefore, Applicant respectfully submits that Sasaki *et al.* do not anticipate the claimed invention. Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

2. Rejection over Daube et al.

The Examiner asserts that Daube *et al.* disclose a method of detecting the presence of a target molecule. The Examiner asserts that Daube *et al.* teaches synthesizing multiple copies of detectable oligonucleotides through abortive reiterative synthesis on a nucleic acid template and detecting said oligonucleotides.

Solely to advance prosecution, and not in acquiescence of the Examiner's rejection, Applicant has amended claim 136 to recite a method for detecting the presence of a target molecule in a biological or environmental sample.

Applicant respectfully submits that Daube *et al.* do not teach methods for detection of a target molecule in a biological or environmental sample. It is clear that the nucleic acids described by Daube *et al.* are synthetic constructs, and are thus not biological or environmental in origin. Moreover, the nucleic acid construct of Daube *et al.* was not made for the purpose of detecting a target molecule in biological or

environmental samples. Instead, Daube *et al.* were interested in investigating the nucleic acid framework and mechanisms of a functional transcription elongation complex. Daube *et al.* constructed a synthetic RNA-DNA bubble duplex to mimic this framework and describe the synthetic construct as follows:

> It consists of an RNA strand that is 20 nt in length, with the 12 nt at the 3' end being fully complementary to the DNA template strand. The remaining 8 nt are not complementary to the template strand, thus forming the beginning of a free (single-stranded) RNA tail. An additional DNA oligonucleotide serves as the nontemplate strand in the construct. This latter DNA is only partially complementary to the DNA template strand, forming a permanently un-paired DNA bubble that accommodates the complementary portion of the RNA strand and allows it to anneal to the template strand within the bubble.

Id. at p. 1320-21.

Daube *et al.* describe use of this complex *solely* as a tool to probe the properties of a functional elongation complex. For example, Daube *et al.* report that addition of RNA polymerase, dNTPs and Mg^{2+} to the synthetic construct resulted in extension of the RNA and that the transcription was template-directed. *Id.* at p. 1321-22 and Fig. 3. Daube *et al.* also report that the complex is characteristic of an elongation complex because of its resistance to heparin and rifampin. *Id.* at 1321-22. The influence of the duplex length on processivity of various polymerases as well as the effects on processivity of the nontemplate strand in the construct were also investigated. *Id.* at p. 1322-23 and Figs. 4-5.

Daube *et al.* characterize the utility of the synthetic construct as follows:

> The synthetic construct can work as a template and substrate for both the *E. coli* and the T7 RNA polymerases. Although technical considerations provided the initial impetus for this synthetic approach to elongation, it is clear

> that many mechanistic problems can be considered in this way, including questions that cannot be addressed by studying elongation complexes formed by conventional means.

Id. at p. 1323. Daube *et al.* further note the following:

> Our synthetic constructs are equally useful for investigating transcription by T7 RNA polymerase. The RNA synthesis catalyzed by the T7 polymerase is processive on all the constructs that we have used (Fig. 4, lanes 5 to 7).

Id. Finally, Daube *et al.* note that "[o]ther such constructs can be designed to examine many of the functional and regulatory properties of transcription systems." See Abstract. Thus, it is clear that Daube *et al.* report on the investigation of a functional elongation complex using a synthetic nucleic acid construct, and do not disclose detection of target molecules in biological or environmental samples using an abortive reiterative synthesis approach as claimed.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Rejection under 35 U.S.C. § 103

The Examiner rejected claim 140 under §103(a) as being unpatentable over Daube *et al.* in view of Sasaki *et al.* Applicant respectfully traverses this rejection.

According to the Examiner, Daube *et al.* do not explicitly disclose the use of a nucleotide analog for termination. The Examiner asserted that Sasaki *et al.* disclose a method of employing chain terminating nucleotides. The Examiner's position is that it would have been *prima facie* obvious to one of ordinary skill to use fluorescently labeled nucleotide chain terminators, as disclosed in Sasaki *et al.*, in the method of Daube *et al.*

As noted above, Applicant has amended the claims to recite a method for detecting the presence of a target molecule *in a biological or environmental sample.* Therefore, whether or not it would be obvious to use a fluorescent dye terminator in the method allegedly described by Daube *et al.* is not material, because Daube *et al.*, either alone or in combination with Sasaki *et al.*, does not teach or suggest using an abortive reiterative synthesis approach to detect a target molecule in a biological or environmental sample. Daube *et al.* endeavored to investigate properties of a functional elongation complex using a synthetic construct. The entire focus of Daube *et al.* is the use of this synthetic construct to study "mechanistic problems" and the cited art in no way teaches or even suggests that such a construct or a reiterative synthesis method be used to detect target molecules in biological or environmental samples.

Accordingly, Applicant respectfully requests that the Examiner reconsider and withdraw the rejection.

Obviousness-type Double Patenting

The Examiner rejected claims 136-147 for obviousness-type double patenting over various claims of the Applicant's issued patent and copending applications. Specifically, the Examiner rejected the Applicant's claims over the following: claims 1-34 of U.S. Patent No. 7,045,319; claims 26, 27, 103, 112, and 136-139 of copending Application No. 10/488,971; claims 1-22, 32-34 and 44 of copending Application No. 10/976,240; claims 11-27 of copending Application No. 10/425,037; and pending and/or elected claims of Application Nos. 10/600,045; 10/602,045; and 10/607,136.

Applicant respectfully requests clarification of the rejection over claims of Application No. 10/600,045 ("High pressure mercury lamp and lamp unit"), which is abandoned.

Applicant respectfully requests that the Examiner reconsider and withdraw these rejections, or hold the present rejections in abeyance, pending the identification of otherwise allowable subject matter, at which time Applicant will consider filing any necessary terminal disclaimers.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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